How Will Evolving Future Therapies and Strategies Change How We Position the Use of Biologics in Moderate to Severely Active Inflammatory Bowel Disease

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Abstract: Several biological agents have been added to our armamentarium of treatment options for moderate to severely active inflammatory bowel diseases, and this number is expected to only increase in the near future. With our growing understanding of disease mechanisms and pharmacokinetics, we are now able to target several mechanisms of action to achieve key endpoints (steroid-free remission and mucosal healing) associated with improved long-term disease-related outcomes. In this context, concerns arise regarding the optimal positioning of currently available biologics and key biologics in development. In this review, we will discuss the currently available evidence for comparative effectiveness of biological agents approved for the use in moderate to severely active inflammatory bowel diseases, with a focus on practical considerations to be made when using these agents in practice. We will further review novel biological agents and small molecule inhibitors in development and discuss future opportunities through which providers may personalize treatment decisions to achieve optimal treatment outcomes.

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Key Words: biologics, small molecules, biosimilars, comparative effectiveness

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory bowel diseases (IBD) characterized by recurrent episodes of intestinal inflammation and mucosal ulceration.[1–3] Historically, patients with IBD were treated sequentially using steroids and nonspecific immunosuppressive agents (azathioprine, 6-mercaptopurine, and methotrexate) with the intent of reducing disease-related symptoms (diarrhea, abdominal pain, and fatigue). Accordingly, disease monitoring was largely based on the subjective assessment of symptom severity, and individual expectations for treatment outcomes were uncertain and unpredictable.[4–8] When infliximab was approved for IBD, expectations for what outcomes are possible with treatment changed and subsequently the concept of personalized medicine evolved.

Initially, evidence established that using tumor necrosis factor (TNF) antagonists in combination with azathioprine early in the disease course (top down) was more effective than the classic sequential step-up approach in moderate to severely active CD.[9] Then, it was demonstrated that the addition of an immunosuppressive agent to TNF antagonist therapy improves treatment efficacy beyond that seen with TNF antagonist or immunosuppressive monotherapy in naive patients to both therapies, and this improved efficacy is at least in part driven by the prevention of immunogenicity and optimization of biological drug concentrations.[10–12] More recently, it has been established that early combined immunosuppression with frequent monitoring of disease activity and drug concentrations has a substantial impact on treatment-related costs and disease-related complications (hospitalizations, surgeries, and overall complications).[13,14] Efforts have therefore now focused on optimizing individual treatment decisions and biological dosing through frequent monitoring with the intent of achieving clinical endpoints that accurately predict disease-related complications (i.e., mucosal healing).[6,15]

Although considerable strides have been made in the optimization of treatment outcomes for IBD, patients with IBD continue to have a greater per-patient expenditure than many other chronic health conditions in the United States, and most of this cost is driven using biological agents.[16–18] With the growing understanding of the disease mechanisms central to the pathogenesis of IBD, a surge of innovation has occurred with the development of several new classes of biological agents, which are in

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various phases of development or introduction into clinical practice. This, coupled with the increasing potential to offset the natural progression and disease complications through personalized therapeutic decisions, will result in a substantial increase in the use of biological agents among patients with IBD over time. The exact positioning and integration of currently available biologics and key biologics in development, the impact they will have on disease outcomes, and the optimal approach to monitoring and adjusting these therapies, however, remains to be determined. In this review article, we will discuss the comparative effectiveness of currently approved biologics and key biologics in development for IBD. We will further discuss the importance of drug concentration monitoring, treatment adherence, and how providers may optimize these 2 factors. Finally, we will highlight future opportunities to engage in personalized medicine and the evolving role of biosimilars.

TNF ANTAGONISTS AND VEDOLIZUMAB: COMPARATIVE EFFECTIVENESS OF CURRENTLY APPROVED BIOLOGICS

When comparing efficacy across agents and trials, we have 2 ways to accomplish this, direct and indirect comparisons. Direct comparisons of biologics through large well-powered randomized head-to-head trials are yet to be conducted within IBD, and therefore, we must rely on indirect treatment comparisons. Network meta-analyses (NMAs) can help assess comparative effectiveness of multiple interventions and synthesize evidence across a network of randomized controlled trials (RCTs), by simultaneous analysis of direct evidence (from head-to-head trials of active agents) and indirect evidence (from RCTs comparing treatments of interest with a common comparator, usually placebo), to calculate a mixed effect estimate as the weighted average of the 2. Such a technique can improve the precision of the estimate (compared with direct evidence alone) and also allows estimation of the comparative efficacy of 2 active treatments, even if no studies directly compare them. However, NMAs do rely on the assumption that no significant differences exist between trials or between common comparator populations (similarity assumption).[19,20] Such an assumption may not be adequately satisfied in trials of biological agents for IBD, because of considerable differences in study design, patient population, co-interventions, and outcome assessment for trials of different biologics. Therefore, caution must be exercised when interpreting results of NMAs of biological agents in IBD.

Crohn's Disease

Induction of Clinical Remission

When considering pivotal RCTs of currently approved biologics for luminal moderate to severe CD, within-study treatment effect size (delta between intervention and placebo) for induction of clinical remission (Crohn's Disease Activity Index [CDAI] <150) is larger with TNF antagonists as compared with vedolizumab, with infliximab and adalimumab appearing to have the greatest measurable treatment effect size[21–25] (Fig. 1). A series of recent indirect treatment comparisons have used the statistical technique of Bayesian NMAs to infer on these comparisons across these trials and have generally suggested that infliximab and adalimumab may be superior to certolizumab pegol and vedolizumab for induction of remission.[26–28] Stidham et al[26] performed an NMA of all TNF antagonists in CD, which included all

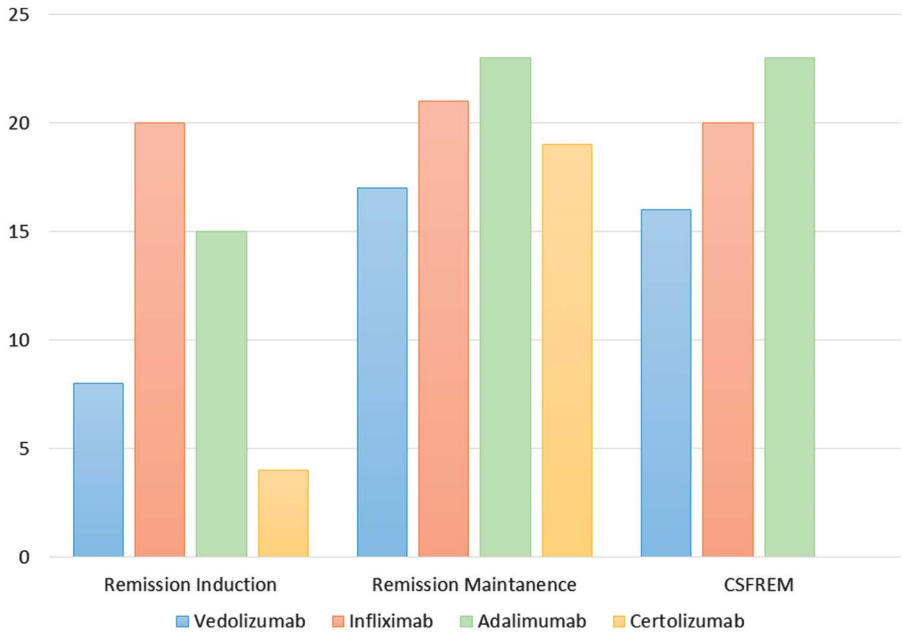

FIGURE 1. Incremental benefit (delta) of currently approved biologics for induction and maintenance of remission in Crohn's disease. CSFREM, corticosteroid-free remission.

patients irrespective of previous biological exposure status, and found that adalimumab may be superior to certolizumab pegol (relative risk [RR] 2.93, 95% credible interval [CrI] 1.21–7.75) for induction of clinical remission, but comparisons between infliximab and adalimumab (RR 1.52, 95% CrI 0.20–17.46) or infliximab and certolizumab pegol (RR 4.29, 95% CrI 0.65–46.09) did not reach statistical significance. Hazlewood et al[28] expanded this search to include vedolizumab and immunosuppressive agents (azathioprine, 6-mercaptopurine, and methotrexate), including trials of concomitant immunosuppressive therapy with TNF antagonists, and similarly found that adalimumab may be superior to certolizumab pegol (odds ratio [OR] 2.1, 95% CrI 1.0–4.6), and the combination of infliximab with azathioprine (OR 3.1, 95% CrI 1.4–7.7) but not infliximab alone (OR 2.1, 95% CrI 0.98–5.5) may be superior to certolizumab pegol. When limiting this analysis to a subset of biological-naive patients with CD, Singh et al[27] found that infliximab was superior to all other biologics (certolizumab pegol: RR 0.24, 95% CrI 0.07–0.73; natalizumab: RR 0.22, 95% CrI 0.06–0.70; vedolizumab: RR 0.23, 95% CrI 0.06–0.78; and ustekinumab: RR 0.10, 95% CrI 0.02–0.52) for induction of remission, with the exception of adalimumab (RR 0.49, 95% CrI 0.11–1.85), but adalimumab was not significantly different when compared with other biologics. Several factors need to be taken into consideration, however, when interpreting and applying these data to routine practice.

The earlier studies for infliximab and adalimumab recruited patients with CD who were more often naive to biological therapy as compared with the nearly 50% of patients with previous biological exposure in the trials for certolizumab pegol and vedolizumab, some of which had failed multiple biologics before recruitment.[23,24] This is of particular importance given the treatment effect size for TNF antagonists is higher among naive patients with CD to biological therapy,[25] and the subanalyses for vedolizumab demonstrated a time-dependent treatment effect for induction of remission in patients who had failed a previous TNF antagonist.[29] Within the GEMINI trial, the treatment effect size of vedolizumab for induction of clinical remission in CD rose from 7% to 16% between week 6 and week 10 of therapy, and this incremental benefit from week 6 to week 10 of therapy was substantially more pronounced in patients who had failed TNF antagonist therapy (3% and 14.5% at week 6 and 10, respectively) as compared with those naive to these agents (19% and 19% at week 6 and 10, respectively).[29] Thus, using an earlier measure of treatment effect size, the meta-analysis by Hazlewood et al[28] may have underestimated the true comparative effectiveness of vedolizumab. Although the study by Singh et al[27] attempted to account for this by limiting the analysis to biological-naive patients and using a 2 to 4 weeks of window after completion of induction therapy for assessing outcome, only infliximab reached statistically significant superiority as compared with certolizumab pegol and vedolizumab within this study. This is in direct contrast to the studies by Stidham et al[26] and Hazlewood et al,[28] where adalimumab, but not infliximab, reached statistically significant superiority to these agents.

Thus, despite using similar studies for comparison, these NMAs yielded different results which are likely due to variations in common comparator groups. A clear example of this is seen within the study of Hazlewood et al,[28] where infliximab is demonstrated to be superior to azathioprine/6-mercaptopurine for induction of remission (OR 2.3, 95% CrI 1.3–5.0), but the combination of infliximab with methotrexate is not (OR 2.1, 95% CrI 0.67–7.9), suggesting that methotrexate may somehow negate the efficacy of infliximab. This brings up an important consideration in that most of RCTs for biologics had a substantial minority of patients (~30%) on concomitant immunosuppressive therapy, and therefore, any indirect comparisons of biological monotherapy or biological combination therapy (concomitant use of an immunosuppressive agent) at the trial level should be interpreted with caution.

Maintenance of Clinical Remission

For maintenance of clinical remission in luminal moderate to severe CD, within-study treatment effect size for maintenance of remission and corticosteroid-free remission was again higher for TNF antagonists, with infliximab and adalimumab achieving the highest within-study treatment effect. The differences between biological agents, however, are much less pronounced as compared with induction of remission data[24,30–32] (Fig. 1). The NMA by Hazlewood et al[28] and Singh et al[27] again demonstrated that infliximab and adalimumab had the greatest treatment effect size and probability of maintaining remission, but the comparative effectiveness data of these 2 meta-analyses were discordant. Singh et al[27] found no single biological to superior to another, but the study by Hazlewood et al[28] suggested that adalimumab and the combination of infliximab with azathioprine were superior to vedolizumab (OR 0.42, 95% CrI 0.22–0.85 for vedolizumab versus adalimumab and OR 0.42, 95% CrI 0.17–0.92 for vedolizumab versus infliximab + azathioprine) and certolizumab pegol (OR 2.5, 95% CrI 1.4–4.6 for adalimumab versus certolizumab pegol and OR 2.6, 95% CrI 1.3–6.0 for infliximab + azathioprine versus certolizumab) for maintenance of clinical remission. The authors concluded that adalimumab monotherapy was superior to certolizumab pegol monotherapy, and infliximab in combination with azathioprine was superior to infliximab or certolizumab pegol monotherapy but not significantly different when compared with adalimumab.

Providers need to remember that there were differences in designing the maintenance phase of RCTs for biological agents (whether randomizing at start of study or re-randomizing only responders to induction therapy). Additionally, within the adalimumab studies, nearly 50% of patients were on concomitant immunosuppressive therapy making comparisons of mono versus combo therapy inaccurate when using these data at the trial level. A recent systematic review aimed at specifically addressing the role of concomitant immunosuppressive therapy with TNF antagonists concluded that, although head-to-head RCTs are lacking for all TNF antagonists, the use of concomitant immunosuppressive therapy is likely beneficial for all TNF antagonists given the clear impact it has on immunogenicity and drug concentrations, a factor known to impact treatment outcomes.[12]

Mucosal Healing, Hospitalization, and Surgery

Mucosal healing has emerged as an important clinical outcome within IBD, and achieving mucosal healing in CD has been associated with a reduced need for corticosteroids, hospitalization, and surgery.[15] Within the ACCENT I trial, mucosal healing rates were noted to be as high as 44% at 1 year with scheduled maintenance infliximab therapy as compared with 18% with episodic therapy.[32] Similar rates were achieved in SONIC, where 6-month mucosal healing rates were considerably higher with infliximab in combination with azathioprine (44%), as compared with infliximab (30%) or azathioprine (16%) monotherapy.[10] For adalimumab, the mucosal healing rates at 1 year within the EXTEND trial were noted to be 24%, and for certolizumab pegol, the mucosal healings rates at 1 year were 14%.[33,34] Mucosal healing was not assessed in the GEMINI trial for CD, and the 1-year rates for mucosal healing with vedolizumab are yet to be determined. It is important to recognize that definitions for mucosal healing varied across studies, and early studies for biologics in IBD did not implore centralized reading, a factor known to impact the quality of scoring and assessment for mucosal healing.[15]

When considering hospitalization and surgery, in the ACCENT I trial, patients with moderate to severe CD treated with scheduled maintenance infliximab were significantly less likely to require hospitalization or surgery as compared with those treated with episodic therapy.[32,35] Similarly, in the ACCENT II trial, patients with fistulizing CD who had initially responded to infliximab and then continued infliximab maintenance therapy required fewer hospitalizations, fewer days in the hospital, surgeries, or procedures as compared with those who received placebo.[36] In 2 separate meta-analyses of RCTs and observational studies, infliximab was associated with a >50% reduction in the need for hospitalizations (RCTs: OR 0.48, 95% confidence interval [CI], 0.34–0.67; observational studies: OR 0.28, 95% CI, 0.18–0.46) and nearly 70% reduction in need for surgery at 1 year (RCTs: OR 0.31, 95% CI, 0.15–0.64; observational studies: OR 0.32, 95% CI, 0.21–0.49).[36–39] Adalimumab has similarly demonstrated a reduction in hospitalization and surgery rates, and within the CHARM trial, the use of maintenance adalimumab in patients initially responding to induction therapy resulted in a reduction in hospitalization at 1 year when compared with placebo (12.6% versus 25.2%). Within the REACT trial, the use of early combined immunosuppression with adalimumab was associated with a significant reduction in hospitalization, complications, and surgery (hazard ratio = 0.74, 95% CI, 0.62–0.87).[13] Long-term data on the risk reduction for hospitalization and surgery with certolizumab pegol and vedolizumab are lacking.

Ulcerative Colitis

Induction and Maintenance of Clinical Remission and Mucosal Healing

Within-study treatment effect sizes (delta between intervention and placebo) for induction of clinical remission (Mayo Clinic score ≤2 and no subscore >1) and mucosal healing (Mayo endoscopic subscore of 0 or 1) in pivotal RCTs of currently approved biologics for moderate to severe UC are larger with infliximab as compared with vedolizumab, with golimumab and adalimumab having substantially lower remission and mucosal healing rates (Fig. 2). For durable remission, corticosteroid-free remission, and mucosal healing with maintenance therapy, the

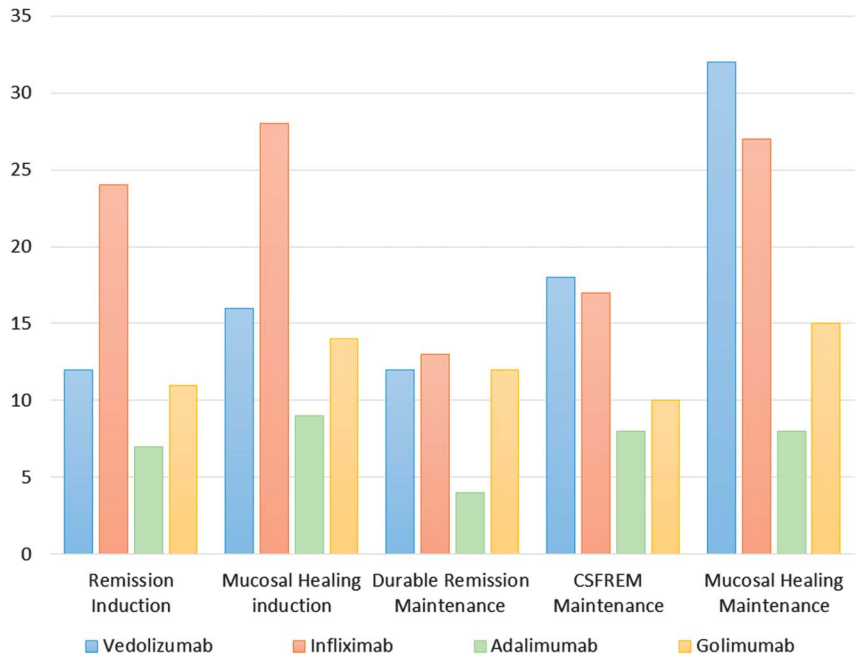

FIGURE 2. Incremental benefit (delta) of currently approved biologics for induction and maintenance of remission in UC. CSFREM, corticosteroid-free remission.

within-study treatment effect sizes for vedolizumab and infliximab are very similar and substantially larger than those seen with adalimumab and golimumab.[40–44]

When pooling data for comparisons across studies and biologics, a meta-analysis by Stidham et al[45] showed trends toward favoring infliximab over adalimumab (RR 2.08, 95% CrI 0.32–12.03) and golimumab (RR 1.18, 95% CrI 0.13–10.63) for induction and maintenance of remission, but these comparisons did not reach statistical significance. Similar to the RCTs for CD, these RCTs varied considerably in patient populations with key difference in previous treatment, particularly TNF antagonist failure. Two recent studies attempted to overcome this by limiting the analyses to biological-naive patients. In the first study by Thorlund et al,[46] adalimumab was less likely to achieve clinical remission (OR 0.42, 95% CrI 0.17–0.97) or mucosal healing (OR 0.46, 95% CrI 0.25–0.86) at 8 weeks, but there was no significant difference between adalimumab and infliximab for week 52 outcomes. The second study by Danese et al[47] observed that infliximab may be superior to adalimumab for achieving clinical response (OR 2.36, 95% CrI 1.22–4.63), clinical remission (OR 2.78, 95% CrI 0.95–8.83), and mucosal healing (OR 2.02, 95% CrI 1.13–3.59) after induction therapy, but infliximab was similar to golimumab and vedolizumab for achieving clinical remission (golimumab: OR 1.84, 95% CrI 0.58–6.92; vedolizumab: OR 1.18, 95% CrI 0.21–6.32), and similar to golimumab for achieving mucosal healing (OR 1.80, 95% CrI 0.96–3.46).[47] Owing to differences in trial designs across agents for maintenance therapy (whether randomizing at start of study or re-randomizing only responders to induction therapy), no inference on comparative efficacy of different biologics for maintenance of remission could be made.

Hospitalization and Surgery

Within the ACT trial, the use of infliximab resulted in a significant reduction in the risk of colectomy at 1 year when compared with placebo (10% versus 17%), and the rates of hospital admissions with infliximab were nearly half that seen with placebo (20 versus 40 hospitalizations per 100 patient years).[48] A post hoc analysis of ULTRA 2 similarly demonstrated that the use of adalimumab induction and maintenance therapy resulted in a significant reduction in hospitalizations both at 8 and 52 weeks of therapy when compared with placebo.[49] A recent meta-analysis of RCTs, however, demonstrated that although infliximab and adalimumab were both associated with a reduction in hospitalizations, only infliximab was associated with a reduction in colectomy rates.[49,50] Data regarding the long-term impact of vedolizumab on hospitalization and colectomy in UC were lacking.

IMPORTANCE OF DRUG CONCENTRATIONS AND ITS IMPACT ON POSITIONING OF CURRENTLY APPROVED BIOLOGICS

When considering how best to position currently available biologics, we must take into consideration whether opportunities exist to optimize treatment efficacy on an individual basis. This is of particular importance given most patients seen in clinical practice would not have qualified for pivotal RCTs used to generate treatment efficacy data, and therefore, the translatability of comparative effectiveness data to routine practice is limted.[51] Monitoring serum drug concentrations is a measure of drug exposure and can be associated with drug efficacy. It is also a measure of bioavailability as the absorption of biologics into the bloodstream is variable, particularly for subcutaneously administered drugs.[52] Monoclonal antibodies typically have a steady-state volume of distribution equal to the plasma volume and are mainly distributed within the central compartment.[53] Although the pharmacokinetics of TNF antagonists and anti-integrin biologics is similar, their mechanism of action, and thus concentration–effect relationship, may be different. Thus, when attempting to understand the optimal positioning of individual biologics, we must consider whether a clear association exists between drug concentrations and treatment outcomes, whether the optimal cut-point for achieving maximal efficacy has been identified, and whether strategies are currently available to monitor and optimize dosing. Therapies with drug monitoring capability, where drug concentrations are clearly linked to improved outcomes, and well designed and studied strategies exist to optimize drug concentrations, will be the favorable first-line agents.

Clinical Impact of Drug Concentrations

For different TNF antagonists, an apparent association between serum drug concentration and various outcome measures has been shown, indicating that this is a class effect. In the IMAgINE-1 study, a serum concentration-efficacy relationship was observed in pediatric patients with moderate to severe CD treated with adalimumab.[54] Similar effects were observed for patients with CD with infliximab as Cornillie et al[55] demonstrated that an adequate infliximab trough concentration of infliximab at week 14 was associated with sustained clinical response. For certolizumab pegol, an association was observed between serum drug concentrations at week 8 and endoscopic response and remission at week 10 in the MUSIC trial.[56] In a post hoc analysis of the ACT 1 and 2 trials, higher concentrations of infliximab were associated with clinical response, remission, and mucosal healing in patients with UC at different time points during induction and maintenance treatment.[57] Similar observations were made in the ULTRA 2 trial, where the proportion of patients with UC in remission increased for higher adalimumab concentration quartiles,[58] and for golimumab, in the PURSUIT trial, already at week 6, a concentration effect was observed in patients with UC.[44] In a retrospective study by Arias et al in 285 patients with UC, adequate infliximab trough concentrations at week 14 predicted relapse-free and colectomy-free survival during long-term follow-up.[59] These and other studies indicate that increasing drug exposure in some patients might lead to better short-term and long-term outcomes.

For vedolizumab, an apparent association was observed between serum drug concentrations and clinical response and

remission at week 6 in CD.[24] This association was less pronounced during the subsequent maintenance phase. A similar observation between serum drug concentrations and clinical response and remission at week 6 was observed in UC.[40] Also here, the association was less pronounced during the subsequent maintenance phase, based on quartile analysis. Interestingly, already after 1 infusion, 95% saturation was observed of $\alpha_4\beta_7$, indicating to some extent that target saturation is achieved even in patients with lower drug exposure. Hence, drug concentrations for vedolizumab may be indicative of some other biological effect beyond blocking the egress of $\alpha_4\beta_7$, expressing lymphocytes from the peripheral blood into the gut.

Optimal Cut-points

The optimal serum drug concentration for TNF antagonists depends on the time point of sampling (induction versus maintenance) and outcome measure (clinical response or remission, C-reactive protein, mucosal healing, etc.).[57] These thresholds can also differ interindividually and intraindividually depending on the disease state and severity, as some patients might require higher drug exposure for induction of remission than to maintain remission. Table 1[55,57,59–70] summarizes different retrospective and prospective studies in IBD that found an association between TNF antagonist trough concentrations and clinical outcomes, and delineated a threshold drug concentration. Typically, a receiver operating characteristic curve analysis was performed to assess the sensitivity and specificity of the obtained threshold in predicting the chosen outcome measure. Interestingly, the concentration thresholds were higher when associated with long-term outcomes (= predictive value) compared with outcomes assessed at time point of sampling (= surrogate marker). Interestingly, the serum concentration–efficacy relationship has been shown to plateau for infliximab.[71] The optimal cut-point for certolizumab pegol and golimumab is yet to be determined.

Strategies Available to Optimize Drug Concentrations

To achieve optimal drug concentrations, providers may implore various strategies, one of which is the upfront use of concomitant immunosuppressive therapy to prevent immunogenicity. Data from the SONIC and UC SUCCESS trials in CD and UC, respectively, showed that the use of concomitant azathioprine led to higher infliximab trough concentrations in patients on combination therapy compared with patients who were treated with infliximab monotherapy.[10,11] Similar observations were made in the COMMIT trial for patients with CD treated with concomitant methotrexate.[72] The mechanism of action is not entirely clear but is likely an additive effect of (1) a synergism between both anti-inflammatory drugs leading to a decreased clearance and (2) an anti-immunogenic protective effect leading to lesser patients developing antidrug antibodies that cause a faster clearance of drug. Comparative effectiveness studies assessing the impact of concomitant immunosuppressive therapy for other biologics is lacking, but a reasonable conclusion to be made is that the concomitant use of immunosuppressive therapy for TNF antagonists

TABLE 1. Drug Concentration Thresholds and Associations with Various Outcome Measures[6,7,55,57,59–68,90]

CD/UC (N)	Drug	Time Point of Sampling	Threshold, μg/mL	Sensitivity %, Specificity %, AUC	Outcome Measure
IBD (128)[60]	IFX	Induction	≥2.0	na, na, 0.76	Long-term clinical response after restart (≥W52)
UC (112)[59]	IFX	W14	≥2.5	81%, 75%, 0.77	Relapse-free survival (6 mo)
IBD (58)[61]	IFX	W14	≥4.0	53%, 75%, 0.64	Persistent remission (W54)
CD (144)[55]	IFX	W14	≥3.5	64%, 78%, 0.75	Sustained clinical response (throughout W54)
CD (85)[62]	IFX	Maintenance	<0.5	86%, 85%, 093	Clinical loss of response
UC (21)[62]	IFX	Maintenance	<0.8	75%, 100%, 0.90	Clinical loss of response
IBD (103)[63]	IFX	Maintenance	<2.0	76%, 82%, 0.68	Absence of clinical remission
CD (327)[64]	IFX	Maintenance	<2.7	63%, 76%, 0.72	CRP >5 mg/L
CD (483)[65]	IFX	Maintenance	≥2.8	53%, 78%, 0.68	Biochemical remission (CRP ≤5 mg/L)
UC (374)[57]	IFX	Maintenance	≥3.7	65%, 71%, 0.71	Clinical response
IBD (46)[66]	IFX	Maintenance	≥8.3	71%, 73%, 0.75	Mucosal healing
CD (81)[67]	IFX	Maintenance	≥5.0	na, na, na	Continued response after IMM withdrawal (FU)
UC (73)[68]	ADA	W4	≥4.6	80%, 56%, na	Clinical response (W12)
UC (73)[68]	ADA	W4	≥7.0	80%, 69%, na	Sustained clinical response (throughout W52)
CD (71)[69]	ADA	Maintenance	≥5.9	68%, 71%, 0.75	Clinical remission
IBD (40)[70]	ADA	Maintenance	<4.9	66%, 85%, 0.77	Absence of mucosal healing

ADA, adalimumab; AUC, area under curve; CD, Crohn's disease; CRP, C-reactive protein; FU, follow-up; IBD, inflammatory bowel disease; IFX, infliximab; na, not available; UC, ulcerative colitis; W, week.

would confer improved efficacy given the clear impact on pharmacokinetics.[12] The impact of concomitant immunosuppressive therapy with vedolizumab will need to be explored further.

Another strategy to optimize drug concentrations has recently emerged, which implores treating based on trough concentrations to maintain adequate exposure and treatment response. In an RCT of 69 patients with CD with secondary loss of response to maintenance infliximab, the implementation of a therapeutic drug monitoring algorithm to guide treatment decisions was compared with empiric dose escalation in terms of cost and efficacy at week 12.[73] Health care costs related to CD were 34% lower for those patients treated in accordance with the algorithm than by infliximab dose intensification. In addition, disease control, as judged by response rates, was similar between both groups. A long-term follow-up of the study showed that the economic benefit of the algorithm-based interventions at infliximab failure is maintained throughout 1 year.[74] In the randomized controlled TAXIT trial including 263 patients with IBD with stable response to maintenance infliximab therapy, dosing based on trough concentrations was compared with dosing based on clinical symptoms and C-reactive protein in terms of efficacy, safety, and cost-effectiveness.[75] This was the first prospective study to confirm the causal relationship between exposure and effect as dose escalation in patients with suboptimal drug concentrations (<3 μg/mL) led to a significant increase in the proportion of patients with CD in remission and a significant decrease in inflammatory markers. Moreover, the study showed for the first time that the infliximab dose can be safely reduced in patients who have supratherapeutic infliximab trough concentrations (>7 μg/mL), which led to 28% drug cost savings. One year after dose optimizing all patients, the proportion of patients who continued infliximab dosing based on trough concentrations did not differ from standard care follow-up, but significantly more patients from the latter group needed rescue therapy because of disease flares. These results indicate a role for therapeutic drug monitoring in clinical practice not only at the time of loss of response but also during routine follow-up in patients to maximize cost-effectiveness of TNF antagonists.

KEY BIOLOGICS AND SMALL MOLECULES IN DEVELOPMENT

Newer biologics and small molecules in phase 3 and 2 development aim to expand on our current treatment options by targeting various pathways within T-cell activation, adhesion, and proinflammatory cytokine activation. Of these various studies, 2 novel agents are anticipated to complete phase 3 trials within the next year, ustekinumab and tofacitinib, and several other agents have shown promising results in phase 2 trials.

Ustekinumab

IL-12 and IL-23 are proinflammatory cytokines that induce Th1 or Th17 differentiation, and these cytokines have been linked to the pathogenesis of CD.[76] Ustekinumab, a fully humanized monoclonal antibody, blocks the biological activity of IL-12 and IL-23 through a common p40 subunit and is currently undergoing phase 3 trials for use in moderate to severely active patients with CD who have failed or are intolerant to TNF antagonists and in TNF antagonists naive patients. Within the phase 2b trials, although an appreciable difference was not noted for achieving induction of clinical remission at week 6 (placebo: 10.6% versus 1 mg/kg: 16%, 3 mg/kg: 15.9%, and 6 mg/kg: 12.2%, $P > 0.2$ for all comparisons), there was a trend toward significance at week 8 (placebo: 10.6% versus 1 mg/kg: 17.6%, $P = 0.11$; 3 mg/kg 18.2% $P = 0.08$; and 6 mg/kg 18.3%, $P = 0.07$). Furthermore, among those who had initially responded to induction therapy, ustekinumab maintenance therapy (90 mg at weeks 8 and 16) resulted in a higher rate of clinical remission (41.7% versus 27.4%, $P = 0.03$) and steroid-free remission (30.6% versus 17.8%, $P = 0.048$) when compared with placebo at week 22.

Mongersen

Another cytokine linked to the pathogenesis of mucosal inflammation in CD is transforming growth factor (TGF)-β1. TGF-β1 is an immunosuppressive cytokine that functions as a negative regulator of T-cell immune responses. Within CD, it has been demonstrated that SMAD7, an inhibitor of TGF-β1 signaling, is overexpressed in patients with CD and inhibition of SMAD7 restores TGF-β1 signaling, and allows for it to inhibit cytokine production.[77] Accordingly, SMAD7 offers a potential therapeutic target for managing CD-related mucosal inflammation. Mongersen, an oral SMAD7 antisense oligonucleotide, has recently completed phase 2 studies and will soon be evaluated in phase 3 investigation.[78] Within the phase 2 trial, the proportion of patients who achieved clinical remission by day 15 and maintained clinical remission for at least 2 weeks was significantly higher in the 160 mg (65%) and 40 mg (55%) groups, as compared with the 10 mg group (12%, $P < 0.001$) and placebo (10%, $P < 0.001$). The proportion of patients in clinical remission at day 84 was similarly significantly higher in the 160 mg (67%) and 40 mg (63%) groups as compared with the 10 mg (29%, $P < 0.001$) and placebo (21%, $P < 0.001$).

Tofacitinib

Traditionally, biological agents have targeted specific receptors or cytokine activity. Tofacitinib, however, is an oral small molecule that selectively inhibits the Janus kinase family, tyrosine kinases that mediate signal transduction for multiple cytokines. By blocking a common signaling molecule used by several pivotal proinflammatory cytokines, tofacitinib inhibits both T-cell and B-cell function while preserving regulatory T-cell function.[79] Although it is not clear that the JAK signaling pathway is dysregulated in the setting of IBD, the efficacy of tofacitinib in rheumatoid arthritis and psoriasis has led investigators to study its potential efficacy in IBD. Phase 2 trials were subsequently conducted for CD and UC.[79,80] Outcomes with tofacitinib in patients with CD was less than ideal, and the phase 2 study failed to meet its primary outcome. In UC, however, rates of clinical remission

with tofacitinib were dose dependent, and patients who were treated with 3 mg (33% remission, $P = 0.01$), 10 mg (48% remission, $P < 0.001$), or 15 mg (41% remission, $P < 0.001$) were significantly more likely to achieve clinical remission at week 8 when compared with placebo (10% remission). In addition, at 8 weeks after therapy, endoscopic remission in UC was achieved in 2% of patients receiving placebo as compared with 18% of patients, receiving 3 mg of tofacitinib ($P = 0.01$), 30% of those receiving 10 mg ($P < 0.001$), and 27% of those receiving 15 mg ($P < 0.001$).

Ozanimod

Another opportunity to modulate inflammation in IBD is through inhibition of lymphocyte trafficking. This can be accomplished by inhibiting ligand interactions at the mucosal level (anti-integrins) or by inhibiting central trafficking through lymph nodes. In order for lymphocytes to leave the lymph nodes, the S1P (sphingosine-1-phosphate) receptors on the surface of lymphocytes must bind to S1P which expressed as a gradient along lymphatic endothelium. By modulating S1P, S1P receptors on the surface of lymphocytes can be internalized and degraded, thereby preventing lymphocyte migration out of the lymph node. This "trapping" reduces circulating effector T-cells, which in turn leads to a selective suppression of the immune system. Ozanimod, an oral S1P modulator, has recently completed phase 2 trials and begun phase 3 trials in UC. Within the phase 2 trial (TOUCHSTONE), the proportion of patients achieving clinical remission at week 8 was higher in the 1.0 mg group (16.4%, $P = 0.0482$) and 0.5 mg group (13.8%, $P = -0.142$) when compared with placebo, and endoscopic improvement was also achieved more often in the 1.0 mg group (34%, $P = 0.002$) and 0.5 mg group (28%, $P = 0.0348$) when compared with placebo (12%).[81]

COMPARATIVE EFFECTIVENESS SUMMARY

Taken together, variations in trial populations, outcome assessment, and heterogeneity across studies make it difficult to directly compare treatment efficacy of biologics currently approved for use in moderate to severely active CD or UC. A reasonable conclusion for CD is that treatment outcomes with infliximab and adalimumab are more well established, and these drugs can be more closely monitored using drug concentration assessments, whereas the efficacy of vedolizumab is time dependent, and it is yet to be determined what impact vedolizumab may have on long-term risks of complications, hospitalization, and surgery. Therefore, in patients who are steroid dependent or resistant, or in those at high risk for disease-related complications (Table 2),[39,82–101] infliximab or adalimumab may be the more appropriate therapy. In patients with CD where time to remission is not as significant of a concern and patients are not felt to be a high risk for disease-related complications, the potential-enhanced safety profile of vedolizumab may be particularly appealing and beneficial in certain populations (i.e., elderly or previous infectious complications). In these settings, vedolizumab for induction and maintenance of remission may be a more appropriate treatment option. For fistulizing or penetrating disease activity in CD, these data are more straightforward, and although other agents have reported fistula healing as a secondary endpoint, only infliximab has been studied with fistula healing as the primary endpoint within RCTs. Therefore, infliximab should remain the first-line agent for all patients with CD with fistulizing and/or penetrating disease activity, and adalimumab should be considered a second-line agent if infliximab fails despite appropriate drug concentrations.[22,23,30,31,102,103]

TABLE 2. Predictors of a More Aggressive Disease Course and Treatment Outcomes in IBD[10,82–99]

Crohn's disease
Perianal, stricturing, or penetrating disease
Small bowel involvement
Younger age at diagnosis and disease duration (>2 yr)
Requirement for steroids at initial diagnosis
Inflammatory burden (extensive and deep ulcerations, high CRP without normalization)
Biological drug concentrations and concomitant immunosuppressive use
Ulcerative colitis
Younger age at diagnosis or gender
Extraintestinal manifestations
High inflammatory burden (CRP, ESR, albumin, extensive colitis, or deep ulcerations on endoscopy)
Hospitalization for a disease flare or need for steroids
Biological drug concentrations and concomitant immunosuppressive use

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

In UC, data would suggest that either infliximab or vedolizumab would be appropriate as the first-line therapy given the similar within-study treatment effect size for induction and maintenance of remission, and mucosal healing. Similar to CD, long-term data for prevention of hospitalization and surgery with vedolizumab are lacking. Therefore, infliximab is likely the more appropriate treatment option for patients at high risk for disease-related complications (Table 2), particularly considering a clear approach exists for optimizing infliximab concentrations and treatment outcomes. Vedolizumab may be an appropriate alternative in certain populations, where the enhanced safety profile may be beneficial.[104] The exact positioning of adalimumab within current treatment algorithms remains unclear. It has been suggested that the reduced efficacy as compared with infliximab is a result of underdosing, and clinical trials are currently underway to address this question through a high-dose induction regimen.

For key biologics in development, although long-term data are needed to understand the exact positioning of these biologics, they have demonstrated significant promise for use as the first-line or second-line therapy. Ustekinumab will likely be a key

biological agent for use in patients with CD who have failed or are intolerant to TNF antagonists, particularly when considering that the existing options for the patients refractory to or intolerant of TNF antagonists are limited, and drug concentration monitoring to optimize treatment efficacy is currently being explored for ustekinumab in other arenas.[105] Mongersen seems very promising given it achieved the highest treatment effect size ever seen induction therapy in CD, but there were no data on mucosal healing, and providers should note that the population of patients enrolled was highly selective, and the drug is designed to only release in the terminal ileum and right colon, limiting its application to a subpopulation of patients with CD. For UC, tofacitinib and ozanimod are oral small molecule inhibitors with significant promise, and they offer the advantage of not being restricted by traditional factors known to impact drug clearance for currently available biologics. Therefore, in patients at high risk for drug clearance, they may provide alternative strategies to optimize treatment efficacy.

FUTURE CONSIDERATIONS: HEALTH CARE REFORM AND TREATING TO A TARGET OF BIOLOGICAL VALUE

Health care has begun to shift away from the current fee for service model, toward a value-based payment model, where providers and health care systems are reimbursed according to treatment outcomes and disease-specific benchmarks (pay for performance).[106–108] With most of costs being driven by biologics in IBD, it can be expected that in the near future, reimbursement for IBD care will be directly linked to how we use our biological agents and how effectively we achieve key long-term outcomes such as clinical remission, mucosal healing, and hospitalization or surgery. Traditionally, our treatment strategies have largely been based on the premise that the value of therapy with biological agents in IBD is for the most part, a function of treatment effect size. The larger the effect size, the greater the value. It is important, however, to consider that treatment effect size is dependent on the population in which the drug is used, and treatment value is also a function of treatment cost and adherence, with adherence being driven by treatment safety and patient preference.[109–112] Therefore, to truly optimize the value of current biological agents and the positioning of future therapies, providers will need to individualize treatment decisions, and IBD will need to shift toward personalized medicine.

Predicting Disease Course: Prescribing the Right Biological Therapy to the Right Patients at the Right Time

Several predictors have been identified for disease progression and/or response to biological therapy (Table 2).[39,82–101] Individually, these factors may help providers when considering how to use and monitor biologics in clinical practice, but they are unable to accurately and consistently predict individual outcomes and/or disease progression. Recent efforts have now transitioned toward the creation of integrated composite bioprofiles that incorporate a patient's genotype, phenotype, clinical course, and pharmacokinetics to predict their individualized natural course of disease progression and the potential anticipated benefit with biological therapies. Siegel et al[113,114] have created a web-based tool for use in adults and children that predicts disease course through the integration of patient characteristics, serologic markers, NOD2 status, and medication exposure. Although the model demonstrated good concordance (adults: concordance index 0.73, pediatrics: concordance index 0.81) when validated against internal and external cohorts, models that built on well-phenotyped prospective cohorts enrolled at the time of diagnosis are still needed.

The mechanism of action of TNF antagonists in IBD is a combined additive effect of both systemic and local functions, and therefore, local monitoring of TNF in tissues may provide predictive capability for treatment outcomes.[115] In a cross-sectional study in 30 patients with IBD treated with either infliximab or adalimumab, TNF and TNF antagonists concentrations in serum were compared with concentrations in tissue biopsies and correlated with endoscopic and histological disease activity.[116] A positive correlation was found between TNF antagonists in serum and tissue for uninflamed, but not for inflamed tissue. This approach could similarly be applied to other biologics, where serum or tissue levels of receptors and ligands (i.e., MadCAM-1)[117] could be measure to determine treatment efficacy and optimization.

Optimizing Adherence: Comparative Effectiveness of Treatment Durability

The efficacy of biological agents is significantly impacted by the ability of patients to remain on therapy for long term. Providers must therefore balance the available data on treatment efficacy against treatment safety and "durability." A recent meta-analysis attempted to quantify this by assessing treatment durability or the likelihood that a patient will stay on therapy.[118] By comparing the number of patients who discontinued therapy against the expected efficacy, the authors created a new metric of treatment durability (number needed to discontinue/number needed to treat). They were able to demonstrate that biological therapies have a higher durability when compared with immunosuppressive agents (azathioprine, 6-mercaptopurin, and methotrexate) in CD, and among biologics' antitrafficking agents carried the greatest likelihood for durability given their enhanced safety profile. Although this novel approach to categorizing treatment durability is promising, these data are obtained solely from RCTs imploring strict inclusion criteria, and future comparisons will need to assess treatment durability in the community setting while accounting for other factors known to impact adherence (access to care and mental health).

Reductions in Costs: Positioning of Biosimilars

Biosimilar TNF antagonist monoclonal antibodies are currently under development, and a recent biosimilar of infliximab (CT-P13) has been approved for use in several international communities. The main advantage of these agents is the reduction in cost associated with their use, and if bioequivalence and

interchangeability can be demonstrated in patients with IBD, it is estimated that biosimilars may result in a 40% reduction in treatment-related costs.[119] Given current guidelines only require in vitro data on similarity to the reference product and far fewer clinical studies are needed for biosimilars, the approval of these agents may create an opportunity for providers to further optimize treatment efficacy through approaches that have traditionally been limited by treatment costs (i.e., early use of biological agents in patients with mild to moderate disease activity and/or the combination of highly selective biological agents with distinct mechanisms of action, anti-integrins, and TNF antagonists, for the induction and/or maintenance of clinical remission and mucosal healing). However, interchangeability will need to be demonstrated in robust clinical trials for these agents to reach their full potential for cost reduction.

SUMMARY

In conclusion, evolving treatment strategies and biological therapies offers an opportunity to optimize disease outcomes in moderate to severely active IBD, but providers will need to consider their relative comparative effectiveness and pharmacokinetics when using them in practice. Therapies with an established impact on short-term (response, remission, and steroid withdrawal) and long-term (hospitalization and surgery) outcomes, with drug monitoring capability where drug concentrations are clearly linked to improved outcomes, will be the favorable first-line agents. In certain populations, the enhanced safety or pharmacokinetic profiles of newer biologics and small molecule inhibitors may be advantageous. Ultimately, treatment algorithms will need to shift toward a personalized approach, where individual preferences, safety profiles, phenotypes, and treatment predictors are integrated into therapeutic decisions and monitoring in an effort to optimize the value of these agents.

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